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ORIGINAL ARTICLE

Risk index score for bacteremia in febrile neutropenic episodes in children with malignancies

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Summary

Purpose: *To prospectively determine risk factors for bacteremia in febrile neutropenic children with malignancies.*

Patients and methods: *We studied 199 episodes of febrile neutropenia in 80 children with malignancies, treated by conventional chemotherapy for a 4-year period (2000 - 2004). A standardized computer database with a set of variables for each febrile neutropenic episode was used. C-reactive protein (CRP) was measured at the first febrile episode and on the 3rd and 5th day from the beginning of antibiotic therapy by immunoturbidimetric method. Blood cultures were taken at the onset of fever and before initiation of antibiotic therapy.*

Results: *Multivariate logistic regression analysis determined 5 variables as independent risk factors for bacteremia: the underlying malignant disease (leukemia, non - Hodgkin's lymphoma / NHL, stage IV), chills, perianal cellulitis, presence of central venous catheter and CRP rise ≥34.5 mg/L between the onset of fever and the 3rd day of empiric antibiotic therapy. Thus we identified a low-risk group for bacteremia of 19.1%.*

Conclusion: *Serial measurement of CRP allows for definite risk stratification of febrile neutropenic episodes on the 3rd day from the onset of fever. The low-risk group could be eligible for sequential empiric antibiotic therapy.*

Key words: bacteremia, children, febrile neutropenia, malignancies, risk stratification

Introduction

In the era of aggressive chemotherapy the survival rate of the children with acute leukemias, lymphomas and solid tumors has substantially increased, but infectious complications have become a major cause of morbidity and mortality in this subgroup of immunocompromised patients. The most frequently observed infectious complication of chemotherapy is febrile neutropenia (FN) and the leading cause of death is bacterial infection, followed by invasive mycoses. Talcott et al. first recognized in adults that FN is a heterogeneous syndrome occurring in patients with different susceptibility to infections and risk for complications and death during the neutropenic period [1]. Since then, a large scale of well-designed prospective studies has been carried out in an attempt to find objective criteria, easily assessable in the first 24 h from the onset of FN that could divide patients with FN into low-, intermediate- and high-risk groups according to the expected severity of the infection and probability of bacteremia [2-4]. This risk-adapted approach could possibly tailor the empiric antibiotic therapy (antibiotics' combination or monotherapy, parenteral in the first days followed by oral administration later), as well as the place of its administration (inpatient or early discharge or even outpatient treatment) [5].

Nowadays IDSA (Infectious Diseases Society of America) recommendations for risk stratification propose the FN MASCC (The Multinational Association for Supportive Care in Cancer) score in adult patients with malignant diseases and Klaasen et al. prediction

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rule for significant bacterial infection in children [6,7]. Overall, there are fewer published studies concerning risk stratification of FN in children than in adults and they have been conducted mostly on a single-centre basis [5]. Most of these studies set bacteremia or "significant bacterial infection" as an endpoint for determination of the high-risk group.

This prospective study was conducted to determine the risk factors for bacteremia in febrile neutropenic children that could be easily assessed in the first days from the onset of FN and based on logistic regression analysis to construct a risk index score for prediction of bacteremia.

Patients and methods

Patients

We studied prospectively 199 consecutive episodes of FN in a 4-year period (2000 - 2004), occurring in 80 children (42 boys and 38 girls) with leukemias, NHL and solid tumors. All patients were treated at the Pediatric Oncohematology Department at the University Hospital in Plovdiv, Bulgaria, and had received only conventional chemotherapy. The study was approved by the local ethics committee. The mean age of the study group was 8.4±0.4 years (range 4 months - 19 years). Forty-two (21%) episodes of FN occurred in patients below 3 years of age. The selection criteria for enrollment in the study were as follows: patients with malignancies on chemotherapy; absolute neutrophil count (ANC) ≤500/mm³ and single axillary temperature ≥38.3° C or 38° C persisting in 2 measurements within one hour; ANC 500-1000/ mm³ and expected decrease in the next 24-48 h as a result of the previously administered chemotherapy [8]. Patients re-entered the study if they developed a new FN episode (after an interval of more than 7 days from the previous one) [9]. Patients were excluded if they had already received antibiotic therapy in the last 72 h because of suspected infection or if the fever occurred during or in the following 6 h after infusion of potentially pyretogenic substances or blood transfusions [10,11].

Definitions

We analysed the highest value of the axillary temperature for the 12-h period before the initiation of empiric antibiotic therapy. Every other day with temperature ≥37.5° C after the initiation of empiric antibiotic therapy was considered a febrile day [12]. Primary bacteremia was defined as infection, proven in the blood cultures taken in the first 48 h from the beginning of empiric antibiotic therapy. Secondary or breakthrough bacteremia was defined as bacteremia caused by other bacteria and occurring more than 48h after the beginning of antibiotic therapy and up to 2 weeks later [13]. Only primary bacteremias were analysed. Bacteremia was regarded as polymicrobial when more than one bacterial organism were cultured in the blood in the first 48 h [14,15], and mixed infection in cases of concomitant bacterial and fungal etiology [16]. Complex bacteremia was defined as bacteremia associated with localized infections of the lungs, liver, spleen, kidneys, intestine, bones and joints, heart, central nervous system, abscesses, cellulitis more than 5 cm in diameter, or soft tissue infection with necrosis [14]. Localized infections were summarized as "infectious focus" and analysed as a separate variable. Hemodynamic instability was diagnosed as arterial blood pressure below 5th percentile of the age-adapted values and/or capillary refill above 3 seconds.

Methods

Standardized computer database was used with the following variables for each FN episode: age, sex, kind of malignancy, presence of remission, steroid therapy in the last 30 days, consecutive number of FN episode, post therapeutic day of occurrence of fever, preceding antibiotic therapy in the last 2 weeks, antibacterial and antifungal prophylaxis, growth factor administration, outpatient or inpatient occurrence of FN, severity of neutropenia, duration of neutropenia preceding fever, total duration of neutropenia, severity of monocytopenia (absolute monocyte count ≤ 100 cells/mm^3), the highest value of fever 12 h before the initiation of empiric antibiotic therapy, duration of fever, presence of chills, mucositis and its grade according to WHO grading system, presence of clinically-documented infection (pulmonary infiltrate, enterocolitis, typhlitis, perianal cellulitis and other rare infectious localizations), hemodynamic instability, presence of central venous catheter (CVC), CRP values at the onset of fever, on the 3rd and 5th day after initiation of antibiotic therapy, and the degree of CRP rise between the first 2 measurements, values of blood urea nitrogen, bilirubin, aminotransferases, total serum protein and serum electrolytes blood culture results.

CRP was measured at the first fever occurrence (CRP1) and, depending on its duration, on the 3rd (CRP3) and 5th (CRP5) day from the beginning of antibiotic therapy by immunoturbidimetric method on clinical-chemical analyzer (Konelab 60i; kits of Ther-

mo Electron Corporation, USA, no. 981699). Values above 10 mg/L were accepted as elevated.

At the onset of FN and before initiation of antibiotic therapy blood cultures were drawn from a peripheral vein or each CVC lumen and injected directly into a culture bottle (BACTEC Peds plus, Becton Dickinson Diagnostic Systems, Sparks, USA). In cases of persistent fever blood cultures were repeatedly drawn every other day. A fluorescent automatic system for continuous monitoring (BACTEC 9240, Becton Dickinson Diagnostic Systems, Sparks, USA) was used with protocol period 5 days.

Subsequently to blood culture sampling, empiric antibiotic therapy started: 3rd generation cephalosporin monotherapy in 156 (78.4%) FN episodes, or combination therapy in 43 (21.6%) episodes. Indication for combination therapy (cephalosporin + aminoglycoside [amikacin] or glycopeptide [teicoplanin]) was a clinical suspicion of severe infection or hemodynamic instability and presence of CVC.

Statistical analysis

Comparison of the proportions of the qualitative variables between groups was performed by Pearson's chi-square and Fisher's exact test (or Student's t-test). The quantitative variables were presented as mean±SE. Quantitative variables were compared between 2 groups by independent t-test or Mann-Whitney U test for non-parametric distribution, and for more than 2 groups - by One-Way ANOVA with Bonferroni's correction or Kruskal-Wallis H for non-parametric distribution. Mean CRP values at the onset of fever and on the 3rd and 5th day were compared by Wilcoxon rank test. Cut-off values for CRP were determined by receiver operating characteristic (ROC) curve analysis. Correlations between variables were examined by Pearson's and Spearman's coefficients. Univariate logistic regression analysis was carried out for all variables potentially associated with bacteremia and relative risk (RR) with 95% confidence interval (CI) was calculated for the significant variables ($p \leq 0.05$). Independent risk factors for bacteremia determined on multivariate analysis were used to create a risk index score by adding the number of factors for each patient. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for the logistic regression model. The area under the ROC curve was calculated to determine the discriminatory power of the risk index. Data were analysed with SPSS (Statistical Program for Social Science, Chicago, Illinois) software and MedCalc software for ROC curves' analysis.

Results

Characteristics of FN episodes

The hematological characteristics and grade, duration and causes of fever in the studied 199 FN episodes are shown on Table 1.

Primary bacteremia was proven in 63 (31.6%) FN episodes and was caused in 42 (66.7%) episodes by Gram (+) and in 21 (33.3%) by Gram (–) pathogens. In 2 (3.2%) of the episodes bacteremia was polymicrobial: *coagulase-negative Staphylococcus (CNS)+A.baumanii* and *P.aeruginosa+A.baumanii*, and in 4 (6.3%) - mixed infection: *CNS, P.aeruginosa, E.coli, S.maltophylia*, associated with *Candida spp*. Complex bacteremia was diagnosed in 25 FN episodes (39.7% of the primary bacteremia episodes).

The etiology of bacteremia, based on the number of the FN episode is shown on Figure 1. Gram (–) bacteremias accounted for only 10% of all first bacteremic episodes, whereas they constituted 51% of the cases in subsequent episodes. There was no correlation between the sequence of FN episode and presence of bacteremia, but statistically significant correlation was found with the Gram (–) etiology of bacteremia (r: 0.5; p=0.002).

CRP values

Comparison of CRP values from the 3 consecutive measurements between groups of FN (unexplained

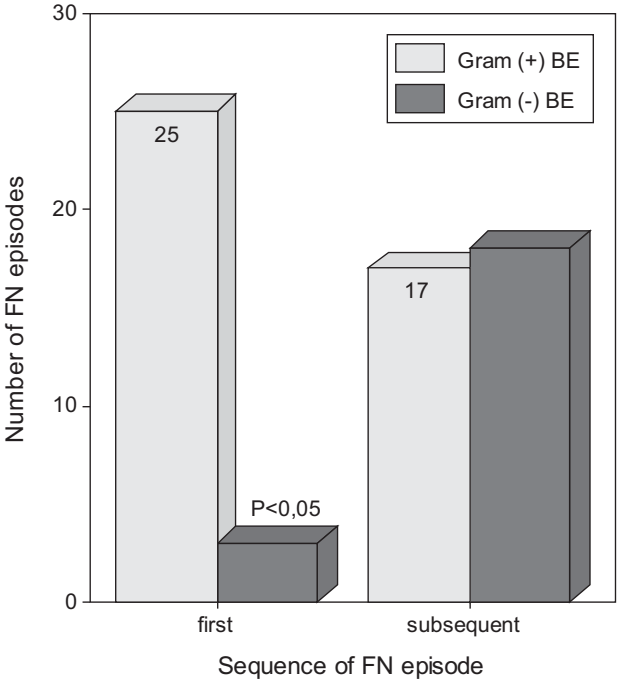

Figure 1. Etiology of bacteremia based on the consecutive number of febrile neutropenic (FN) episodes. BE: bacteremic episodes.

Table 1. Characteristics of febrile neutropenia episodes

Parameter	*Groups*	*FN episodes n (%)*
Kind of malignancy	Leukemia, NHL-stage IV	140 (70.4)
	Solid tumors, NHL stage I-III	59 (29.6)
ANC (per mm³)	≤100	121 (60)
	101 - 499	78 (40)
AMC* (per mm³)	≤100	143 (72)
	>100	40 (20)
N of febrile days	1-2	79 (40)
	3-4	51 (25)
	≥5	69 (35)
T (º C)**	38-39	142 (71.5)
	>39	53 (26.6)
Duration of neutropenia preceding the fever (days)	0	89 (44.7)
	1-5	67 (33.7)
	6-15	29 (14.6)
	>15	14 (7)
Total duration of neutropenia (days)	1-5	75 (38)
	6-15	88 (44)
	>15	36 (18)
Groups of FN	Unexplained fever	78 (39.2)
	Bloodstream infections (bacteremia, fungemia)	85 (42.7)
	Clinically or microbiologically proven localized infection	36 (18.1)

FN: febrile neutropenia, ANC: absolute neutrophil count, AMC: absolute monocyte count, T: temperature, NHL: non Hodgkin's lymphoma
*AMC was measured in 183 FN episodes. **In 4 FN episodes patients were hypothermic with other signs of infection

fever [UF], bacteremic episodes and localized infections) is shown on Figure 2. Analysis proved statistically significant difference of CRP3 (p=0.045) and CRP5 (p=0.011) between groups. The highest values of CRP3 and CRP5 were measured in the localized infection group (105±14.3 and 93.1±20.2 mg/L, respectively), followed by CRP3 and CRP5 values in bacteremic episodes (88.8±9.7 and 82.9±8.9 mg/L, respectively). There was no correlation between CRP1, CRP3 and CRP5 and presence of bacteremia. Significant correlation was found only between values of CRP3 and complex bacteremia (r: 0.8, p=0.002).

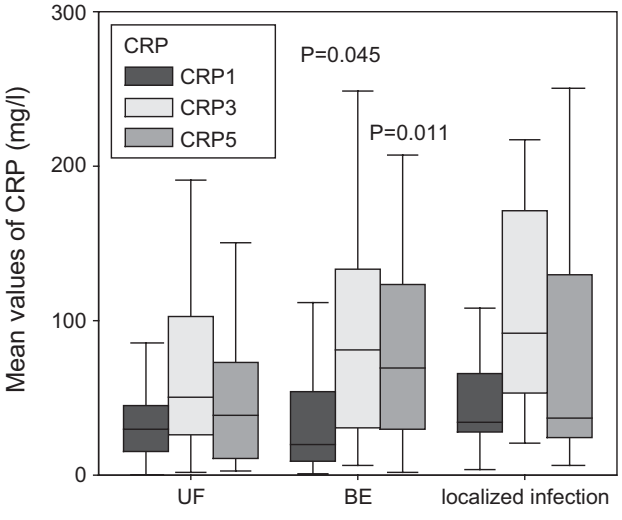

Figure 2. Boxplots of mean values of CRP1 (onset of fever), CRP3 (on the 3rd day) and CRP5 (on the 5th day) in the groups of febrile neutropenia: unexplained fever (UF), bacteremic episode (BE) and localized infection.

Increasing values of CRP3 compared to CRP1 were measured in 106 (53.2%) FN episodes and correlated with the presence of bacteremia (r: 0.6; p=0.005). The rise of CRP from the onset of fever to the 3rd day of antibiotic therapy was more pronounced in bacteremic episodes (48.6±8.6 mg/L) than in UF (14.5±7 mg/L) (F 4.6; p=0.01). By ROC curve analysis we were able to determine a cut-off value of 34.5 mg/L for the degree of the CRP rise from the onset of fever to the 3rd day of empiric antibiotic therapy (CRP3-CRP1). This cut-off value showed 75% sensitivity and 60% specificity for bacteremic episodes and complex bacteremia (AUC 0.7; 95% CI: 0.6-0.8).

Factors associated with bacteremia

The variables associated significantly with the

Table 2. Risk factors for presence of bacteremia

Variable	*% FN episodes with the variable**	*Univariate analysis*	*Multivariate analysis*	
		p-value	*RR (95% CI)*	*p-value*
Leukemia/NHL-stage IV	85	0.003	3.9 (1.7-9)	0.002
Inpatient onset of FN	86	0.009	3 (1.3-6.9)	0.111
Chills	13	0.036	3.4 (0.9-11.9)	0.052
Perianal cellulitis	8	0.004	11.3 (1.2-104.8)	0.026
Fever ≥ 39° C	32	0.014	1.9 (1-3.9)	0.197
Age ≤ 3 years	31	0.014	2.2 (1-4.7)	0.225
Presence of CVC	14	0.002	5.7 (1.5-20.9)	0.017
Degree of CRP rise (CRP3-CRP1) ≥34.5 mg/L	44	0.001	3 (1.6-5.9)	0.001
Clinically proven infectious focus	40	0.004	2.5 (1.3-4.8)	0.921

NHL: non Hodgkin's lymphoma, FN: febrile neutropenia, CVC: central venous catheter, RR: relative risk, CI: confidence interval
*As a % from bacteremic episodes (n=63)

presence of bacteremia by the univariate analysis, and coded as binary values were included in multivariate logistic regression analysis (Table 2).

By multivariate analysis we determined 5 variables as independent risk factors for bacteremia: the underlying malignant disease (leukemia, NHL-stage IV), chills, perianal cellulitis, presence of CVC and degree of CRP rise ≥34.5 mg/L between the onset of FN and the 3rd day of empiric antibiotic therapy. This logistic regression model showed sensitivity 93%, specificity 25%, negative predictive value 89% and positive predictive value 36% for the presence of bacteremia (x^2: 44, -2 log likelihood: 200, Cox & Snell R square: 0.2).

The low-risk group (no risk factor) comprised 19.1% from all FN episodes. The frequency of bacteremia progressively raised with increase in the number of risk factors - from 10.5% in the low-risk group to 80% in the group with 3 risk factors (Table 3). In the one-risk factor group the type of the underlying malignancy prevailed - in 88 (83.8%) FN episodes, followed by the degree of CRP rise (CRP3-CRP1) in 14 (13.3%) FN episodes, chills in 2 (1.9%) FN episodes and presence of CVC in 1 (1%) FN episode.

The predictive model was validated in a combined group of 74 FN episodes-53 reviewed retrospectively (January 1998 - December 1999) and 21 prospectively (August 2004-February 2005). Bacteremia was proven in 28 (37.8%) FN episodes from the validation set. Gram (+) bacteremias prevailed with 20 FN episodes (71.4% of all bacteremic episodes). Patient distribution according to the type of the underlying malignancy was similar to that in the derivation set-55 (74.3%) FN episodes occurred in leukemias and NHL-stage IV and 19 (25.7%) in solid tumors. Chills were present in 15 (20.3%) episodes and perianal cellulitis in 2 (2.7%). CVC was in place in 10 (13.5%) of the FN episodes and CRP increased above the cut-off value of 34.5 mg/L in 22 (29.7%).

The observed frequency and the RR for bacteremia according to the number of risk factors in the validation set are shown on Table 4 and are similar to those in the derivation set.

Risk index score for bacteremia (RISB)

On the basis of the logistic regression model we constructed RISB and similarly to other studies we gave

Table 3. Observed frequency and relative risk for bacteremia according to number of risk factors in FN episodes. This Table was generated by crosstabs 2×2 statistics comparing low-risk group with other groups

Number of risk factors	*FN episodes n (%)*	*Frequency of bacteremia (%)*	*RR (95% CI)*
0	38 (19.1)	10.5	1
1	105 (52.7)	22.8	5 (1.1-22.7)
2	46 (23.2)	58.6	13.3 (2.9-61.8)
3	10 (5)	80.0	52.5 (6.2-439)

FN: febrile neutropenia, RR: relative risk, CI: confidence interval

Table 4. Observed frequency and relative risk for bacteremia according to number of risk factors in febrile neutropenia episodes from the validation set. This Table was generated by crosstabs 2×2 statistics comparing low-risk group with other groups

Number of risk factors	*FN episodes n (%)*	*Frequency of bacteremia (%)*	*RR (95% CI)*
0	12 (16.2)	8.3	1
1	32 (43.2)	21.9	6.5 (0.7-54.6)
2	19 (25.7)	63.2	18.8 (1.9-178.7)
3	10 (13.5)	70.0	25.6 (2.2-298.4)
4	1 (1.4)	100.0	

FN: febrile neutropenia, RR: relative risk, CI: confidence interval

Table 5. Risk index score for bacteremia

Variable		*Points*
Kind of malignancy	Solid tumors, NHL stage IV	0
	Leukemia/NHL stage IV	1
Chills	absent	0
	present	1
Perianal cellulitis	absent	0
	present	1
Presence of central venous catheter	absent	0
	present	1
Degree of CRP rise from onset of fever to 3rd day (mg/L)	<34.5	0
	≥34.5	1

1 point to each of the factors included in it because of the close RRs [18-20]. So the RISB could vary from 0 (no risk factor) to 5 (all risk factors present) (Table 5).

In the validation set RISB differed significantly between bacteremic episodes (2±0.2) and non-bacteremic episodes (1±0.1) (t: 4.7; $p<0.001$). So we were able to divide FN episodes in two risk groups: low-risk (RISB 0 and 1) and high-risk group (RISB ≥2).

The ROC curve analysis of RISB in the validation set showed AUC: 0.78; 95%CI: 0.67-0.87. RISB ≥2 has 71.4% sensitivity, 78.3% specificity, 66.7% positive predictive value and 81.8% negative predictive value for presence of bacteremia.

Discussion

Mono- and polymicrobial bacteremias account for 10-27% of the FN episodes and are usually regarded as a feature of a high-risk episode [21]. The etiology of bacteremias has changed significantly during the last decades with prevailing Gram (+) organisms (*CNS* and *Streptococcus α-haemolyticus)* according to EORTC studies [22]. The absence of signs of infection on physical examination does not rule out life-threatening bacteremia in the setting of profound neutropenia. Also no rapid, sensitive and specific laboratory test exists for prospective identification of bacteremic episodes and hence tailoring antibiotic.

The present study is a prospective evaluation of the probable risk factors for bacteremia in a group of 199 consecutive FN episodes, treated at one center with standardized approach. From the published prospective and retrospective studies in children with malignancies we identified the following risk factors for bacteremia in FN episodes: 1) Hematological malignancy as underlying disease [23]; 2) Chills [23]; 3) Proven infectious focus - clinically or by X-ray [24]; 4) Fever ≥39° C at the onset of FN [3]; 5) Use of CVC [25]; 6) Absolute monocyte count <100/mm^3 [7,26]; 7) Hemodynamic instability [3,23]; 8) Long-lasting neutropenia preceding the fever [3]; 9) Previous FN episodes [24]; 10) Values of CRP ≥90 mg/L at the onset of fever [19]. All of them were included in the univariate analysis, and the first 5 proved to be statistically significant.

From all studied infectious foci, only perianal cellulitis proved to be independent risk factor for bacteremia. The established frequency of perianal cellulitis in the present study was comparable to the reported in the literature - about 5% [27]. Perianal cellulitis was the factor with the least index events - 5 bacteremic episodes in the study group – but this number is considered adequate for multifactorial analysis [20].

The predictive role of absolute monocyte count <100/mm^3 was not significant in our study. The same results regarding the absolute monocyte count on admission for FN were demonstrated by Santolaya et al. in a multicenter study of 447 FN episodes in 257 children screened for invasive bacterial infection [19].

The duration of neutropenia as a risk factor for bacteremia probably influences the statistical significance of the underlying disease and bone marrow involvement by the malignancy, but was not an independent risk factor in our study, similar to the results of Ammann et al. [24].

The sequence of the FN episodes can be used as a criterion for identification of Gram (–) from Gram (+) bacteremias, probably due to the colonization with nosocomial strains as a result of frequent hospitalizations. The predictive value of the consecutive number of the FN episodes for presence of Gram (–) bacteremia was also reported in a retrospective single-centre cohort study of 364 febrile neutropenic episodes in children by Ammann et al. [24].

Studies on CRP values in FN show conflicting results. Santolaya et al. demonstrated that CRP values >40 mg/L discriminated children with bacterial infection on day 1 after the onset of fever with 100% sensitivity and 76.6% specificity [28]. Other studies established that a single measurement of CRP at the onset of fever can not distinguish patients with bacteremia from those with unexplained fever or localized infection as well as Gram (–) from Gram (+) bacteremia [29,30]. CRP rises late in the course of bacteremia and has mainly negative predictive value in serial measurements. This restricts its use as an early predictor of bacteremia in FN [31]. Probable explanation for the inadequate CRP reaction in FN is the minimal tissue damage because of the reduced neutrophil count, as well as the impaired liver metabolic state as a result of chemotherapy. We found that the degree of CRP rise ≥

34.5 mg/L between the onset of fever and the 3rd day was statistically significant. Manian et al. found in a group of 40 adults with neutropenia that an increase of CRP ≥ 50 mg/L between day 1 and 2 after the onset of fever strongly suggested documentable infection with 48% sensitivity and 96% specificity [32]. They also showed that CRP values on days 2 and 3 did not differ significantly, which was the reason to choose measuring CRP on the 3rd day after starting of empiric antibiotic therapy in our study.

A common feature of the published prognostic models for bacteremia in FN in children with malignancies is the aim to increase sensitivity and negative predictive value, which often leads to low specificity, but reduces the frequency of false low-risk group episodes [36]. The present study is characterized by relatively high frequency of bacteremia and we were able to identify a low percentage of the low-risk group (19.1%), comparable to the published by Viscoli et al. in adults [16]. A relative disadvantage of our logistic regression model is the necessity for serial measurements of CRP, which allows definite risk stratification of the FN episodes on the 3rd day from the onset of FN. Having in mind its high statistical significance we would recommend sequential empiric antibiotic approach with switch to oral or even outpatient treatment in the low-risk group on the 3rd day after CRP evaluation.

In conclusion, we propose a risk index score for bacteremia in FN episodes in children with hematologic malignancies and solid tumors, derived and validated in a single-centre prospective study. This model needs to be further tested in large-scale multicenter studies before it is clinically applied for treatment stratification in febrile neutropenic children.

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